

Rabies mAb for PEP : Clinical development experience

Presented by
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SERUM INSTITUTE OF INDIA PVT. LTD.

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FDA Workshop: Developing Rabies Monoclonal
Antibody Products as a Component of Rabies
Post-Exposure Prophylaxis
FDA White Oak Campus,
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Anti-Rabies mAb: Chronology of Development

2003: Research goal of MassBiologics of the University of Massachusetts Medical School:

- Identify human mAb(s) that would be safe, effective and affordable alternative to RIG in places where disease burden is high
 - Neutralize all natural isolates
 - Be of high potency
 - Demonstrate efficacy in *in vivo* hamster model of rabies
- Immunized HuMAb-Mouse[®] (from Medarex now wholly-owned subsidiary of BMS) with rabies vaccine followed by hybridoma production to isolate RMAB1, an IgG1k conformational epitope, antigenic site III-directed antibody to G protein
- 2006: MassBiologics and Serum Institute of India, Pvt Ltd signed an agreement to further develop RMAB1
- *RMAB1, HuMab17C7, RAB1, MBL RAB1 are all synonyms for SII RMAB (Rabishield)*

SII RMAb Neutralizes Broad Panel of Isolates

<i>Rabies virus</i>	SII RMAb	Crucell CR57	Crucell CR4098
CVS-11	+	+	+
Raccoon, SE US	+	+	+
Gray fox, TX	+	+	+
Gray fox, AZ	+	+	+
Arctic Fox, AK	+	+	+
Coyote, TX	+	+	+
Dog/Coyote, TX	+	+	+
Skunk, north central	+	+	+
Skunk, south central	+	-	+
Skunk, CA	+	+	+
Bat, Lasiurus borealis, TN	+	+	+
Bat, Eptesicus fuscus-Myotis spp., CO	+	-	+
Bat, Myotis spp., WA	+	+	+
Bat, Lasiurus cinereus, AZ	+	+	+
Bat, Pipistrellus subflavus, AL	+	+	+
Bat, Tadarida brasiliensis, AL	+	+	+
Bat, Lasionycteris noctivagans, WA	+	+	+
Bat, Eptesicus fuscus, PA	+	+	-
Mongoose, NY/Puerto Rico	+	+	+
Dog, Argentina	+	+	+
Dog, Sonora	+	+	+
Dog, Gabon	+	+	+
Dog, Thai	+	+	+

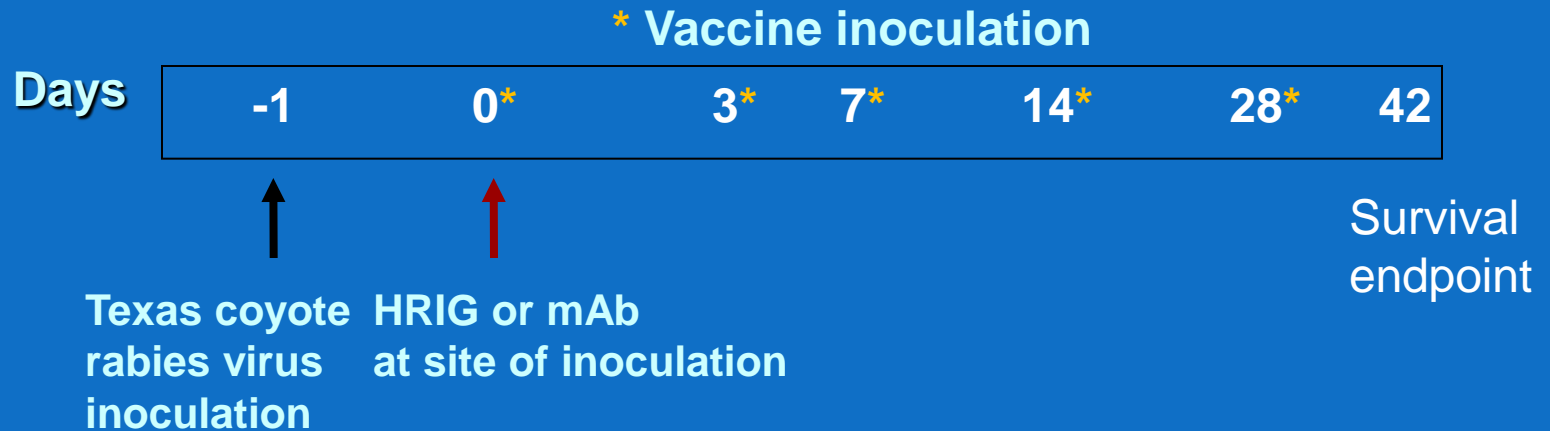
Bakker ABH et al J Virol 2005;79:9062; Sloan SE et al Vaccine 2007;25:2800

SII RMAb Neutralizes Isolates from Asia

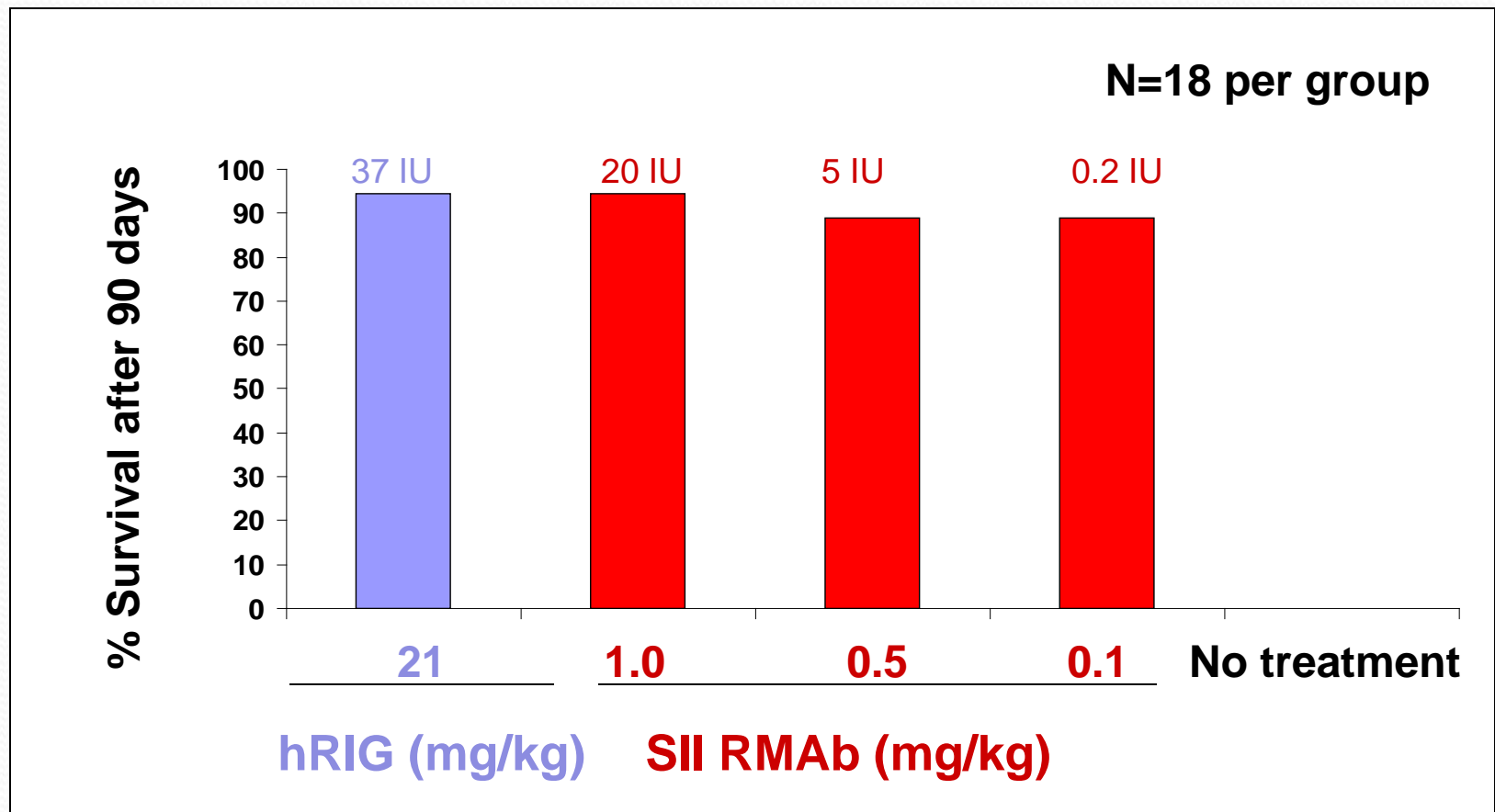
<i>Rabies virus</i>	SII RMAb
ERA	+
Pasteur virus	+
Dog, Nepal 028	+
Dog, Nepal V120	+
Dog, Nepal V123	+
Dog, Nepal V124	+
Dog, Sri Lanka V029	+
Dog, Sri Lanka V112	+
Dog, Sri Lanka V113	+
Dog, Sri Lanka V114	+
Dog, Sri Lanka V115	+
Dog, Sri Lanka V118	+
Dog, India (556)	+
Dog, India (1717)	+
Dog, India (3407)	+
Dog, India (20507)	+
Dog, India (1)	+
Dog, India (2)	+
Dog, India (3)	+
Dog, India (124138)	+
Dog, India (127823)	+
Dog, India (202694)	+
Dog, India (B48)	+
Dog, India (ND)	+
Procyon lotor, Ontario, Canada 1056	+
Procyon lotor, Ontario, Canada 951	+
Procyon lotor, New Brunswick, Canada	+

Hamster Model Used to Assess Protection from Lethal Rabies

In vivo, Post-Exposure Prophylaxis (PEP) experiments conducted at U.S. Centers for Disease Control and Prevention (CDC)

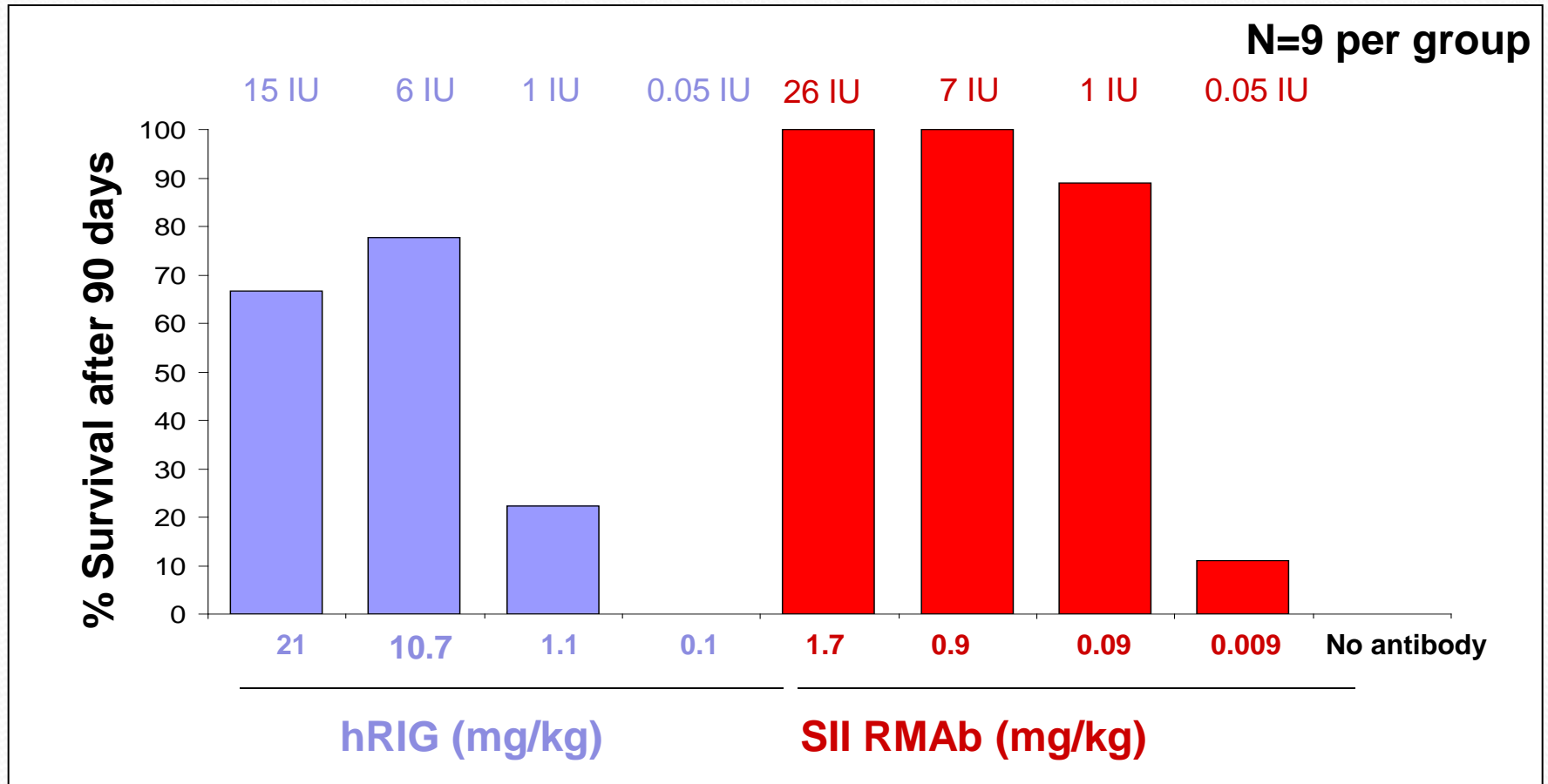


SII RMAb Protects Hamsters in PEP Model



Sloan SE et al Vaccine 2007;25:2800

SII RMAb Alone Protects Hamsters From Rabies



Rabies virus isolate = Texas coyote

Sloan SE et al Vaccine 2007;25:2800

Identification and characterization of a human monoclonal antibody that potently neutralizes a broad panel of rabies virus isolates[☆]

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Abstract

Rabies is a zoonosis that results in millions of human exposures worldwide each year. Human monoclonal antibodies (HuMAbs) that neutralize rabies virus may represent one viable strategy for post-exposure prophylaxis in humans, and have many advantages over current human or equine rabies immune globulin. Transgenic mice carrying human immunoglobulin genes were used to isolate human monoclonal antibodies that neutralized rabies virus. Several HuMAbs were identified that neutralized rabies virus variants from a broad panel of isolates of public health significance. **HuMAb 17C7 was the most promising antibody identified because it neutralized all rabies virus isolates tested. HuMAb 17C7 recognizes a conformational epitope on the rabies virus glycoprotein which includes antigenic site III. HuMAb 17C7 protected hamsters from a lethal dose of rabies virus in a well-established in vivo model of post-exposure prophylaxis.**

Contents lists available at [ScienceDirect](http://www.sciencedirect.com)

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral



G glycoprotein amino acid residues required for human monoclonal antibody RAB1 neutralization are conserved in rabies virus street isolates

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ABSTRACT

Replacement of polyclonal anti-rabies immunoglobulin (RIG) used in rabies post-exposure prophylaxis (PEP) with a monoclonal antibody will eliminate cost and availability constraints that currently exist using RIG in the developing world. The human monoclonal antibody RAB1 has been shown to neutralize all rabies street isolates tested; however for the laboratory-adapted fixed strain, CVS-11, mutation in the G glycoprotein of amino acid 336 from asparagine (N) to aspartic acid (D) resulted in resistance to neutralization. Interestingly, this same mutation in the G glycoprotein of a second laboratory-adapted fixed strain (ERA) did not confer resistance to RAB1 neutralization. Using cell surface staining and lentivirus pseudotyped with rabies virus G glycoprotein (RABVpp), we identified an amino acid alteration in CVS-11 (K346), not present in ERA (R346), which was required in combination with D336 to confer resistance to RAB1. A complete analysis of G glycoprotein sequences from GenBank demonstrated that no identified rabies isolates contain the necessary combination of G glycoprotein mutations for resistance to RAB1 neutralization, consistent with the broad neutralization of RAB1 observed in direct viral neutralization experiments with street isolates. All combinations of amino acids 336 and 346 reported in the sequence database were engineered into the ERA G glycoprotein and RAB1 was able to neutralize RABVpp bearing ERA G glycoprotein containing all known combinations at these critical residues. These data demonstrate that RAB1 has the capacity to neutralize all identified rabies isolates and a minimum of two distinct mutations in the G glycoprotein are required for abrogation of RAB1 neutralization.

SII RMAb - Discovery Conclusion

- Neutralizes all currently identified rabies isolates
- Protects hamsters from challenge with rabies virus with or without vaccine
- Viable replacement for hRIG in PEP
- Strong pre-clinical data paved way for Phase I clinical study

Clinical Development of SII RMAb MBL- SIPL Collaboration

Collaboration and Licensing Agreement Signed	2006
Tech Transfer of RMAB1 Master Cell Bank	2007
SIPL inoculates bioreactor to produce RMAB1	2007
SIPL makes first clinical lot	2008
Phase 1 study begins in India	2009
Phase 2/3 study begins in India	2012
Phase 2/3 study completed	2015
Marketing authorization received	2016

Phase 1 Study: Design & Conduct

- Open-label, dose escalation study
- Simulated PEP regimen
 - MAB + vaccine or HRIG + vaccine
- Safety
 - Assessment of adverse events
 - Laboratory evaluations
- Pharmacokinetics
 - Measure neutralizing antibody activity of HRIG + vaccine or MAB + vaccine
 - Determine MAB dose comparable to HRIG
- Cautious approach used in dose selection:
 - Safety demonstrated with two low dose levels of MAB in 2 subjects each
 - Subsequent enrollment in PEP regimen after review and approval of safety data by IRB
- Different dose levels investigated in combination with rabies vaccine.
- pK parameters assessed with MAB only cohort

Phase I Study : Safety Results

- Two unrelated SAEs during 1 year follow-up period
- 203 non-serious adverse events (AE)
 - 165 (81%) solicited AE related to antibody or vaccine injection
 - 157 (77%) assessed as mild
 - Injection site pain most common event
 - Frequency similar between study cohorts and controls
- No participant with Anti-drug antibody (ADA)

Gogtay et al Vaccine 2012;30:7315

Phase I Study:

Comparison of Immune Response

Study Visit Day									
	0	3	7	14	28	42	56	84	365
Cohort	RFFIT (GMC IU/ml)								
HRIG 20 IU/kg + rabies vaccine	0.220	0.259	0.443	15.3	40.3	48.6	26.5	13.0	2.67
SII RMAb 3.33 IU/kg + rabies vaccine	0.220	0.310	0.243	23.4	25.1	30.1*	16.2	10.7	1.93
	*P < 0.05 by t-test								
	ELISA (GMC µg/ml)								
HRIG 20 IU/kg + rabies vaccine	0.372	0.372	0.436	3.50	12.6	21.1	16.5	11.5	2.67
SII RMAb 3.33 IU/kg + rabies vaccine	0.372	1.20*	1.05**	2.94	9.72	19.6	15.7	8.22	2.21
	*P < 0.0001 by Wilcoxon rank sum, **P < 0.01 by Wilcoxon rank sum								
	RFFIT by Flury LEP strain								
HRIG 20 IU/kg + rabies vaccine	0.059	0.328	0.369	7.90					
SII RMAb 3.33 IU/kg + rabies vaccine	0.044	7.54*	7.53**	12.3†					
	*p < 0.001 by t-test, **p < 0.001 by Wilcoxon rank sum, †p < 0.01 by Wilcoxon rank sum								

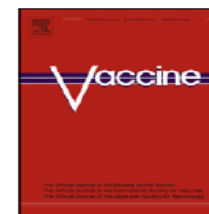
Immunogenicity Features

- GMT by CVS-11 RFFIT comparable between SII RMAb and HRIG cohorts with single timepoint showing a statistically significant difference (Day 42)
- GMC by ELISA and GMT by RFFIT with Flurry LEP strain, at Days 3 and 7 significantly greater in SII RMAb cohort than HRIG
- Seroresponse (RVNA \geq 0.5 IU/ml by RFFIT with **Flurry LEP**) was achieved in all subjects by Day 3 who received SII RMAb, while only one subject in HRIG group had seroprotection Day 7
- Early seroresponse is critical in PEP of Rabies



Contents lists available at SciVerse ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Safety and pharmacokinetics of a human monoclonal antibody to rabies virus: A randomized, dose-escalation phase 1 study in adults[☆]

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ABSTRACT

Background: Rabies is an essentially fatal disease that is preventable with the timely administration of post-exposure prophylaxis (PEP). The high cost of PEP, which includes vaccine and hyperimmune globulin, is an impediment to the goal of preventing rabies in the developing world. Recently a recombinant human IgG₁ anti-rabies monoclonal antibody (SII RMAb) has been developed in India to replace serum-derived rabies immunoglobulin. The present study was conducted to demonstrate the safety of SII RMAb and to determine the dose resulting in neutralizing serum antibody titers comparable to human rabies immunoglobulin (HRIG) when administered in conjunction with rabies vaccine in a simulated PEP regimen.

Methods: This randomized, open label, dose-escalation phase 1 study was conducted in healthy adults at a large tertiary care, referral, public hospital in India. Safety was assessed by active surveillance for adverse events along with standard laboratory evaluations and measurement of anti-rabies antibodies (ADA). Anti-rabies antibody levels were measured by rapid fluorescent focus inhibition test (RFFIT) and ELISA. The study duration was 365 days.

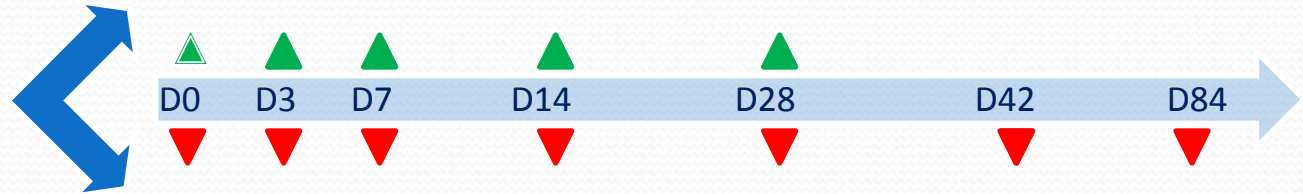
Findings: SII RMAb was well tolerated with similar frequency of local injection site reactions to HRIG. The geometric mean concentrations of rabies neutralizing antibody in the vaccine plus SII RMAb 10 IU/kg cohort were comparable to the vaccine plus HRIG 20 IU/kg cohort throughout the 365-day study period; day 14 geometric mean concentrations 23.4 IU/ml (95% CI 14.3, 38.2) vs. 15.3 IU/ml (95% CI 7.72, 30.3; $p = \text{NS}$), respectively. Future post-exposure prophylaxis studies of SII RMAb at a dose of 10 IU/kg in conjunction with vaccine are planned.

Phase II/III Study Design

Part 1

50 subjects with WHO category III bites to LE only

SII RMAB+Rabivax®
n=25



HRIG+ Rabivax®
n=25

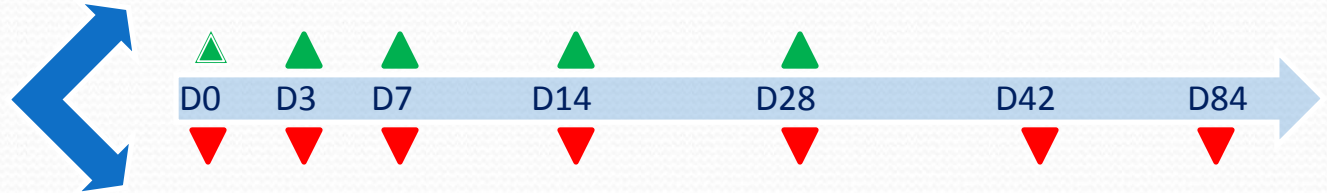
Safety, PK Analysis

Interim analysis (Futility)

Part 2

150 subjects with WHO category III bites (All)

SII MAB+Rabivax®
n=75



HRIG+ Rabivax®
n=75

Safety, PK Analysis

Phase II/III Pivotal Study

Primary Endpoint

- Day 14 GMTs measured by RFFIT of SII RMAb + vaccine compared to HRIG + vaccine given as post-exposure prophylaxis

Pivotal Study: Part 1 (n=50)

- Enrolment started in June 2012 - adults and postmenopausal females with exposure only on lower extremity presenting within 72 hours of bite
- DCGI Submission of safety data of first 10 adults seeking permission to enroll children and women of child bearing age – 31 Dec 2012
- Subject enrolment completed - 14 Jan 2013
- Interim analysis for futility based on D14 RFFIT data performed - 24 Mar 2013
 - Futility not met, DSMB recommends continuation of study

Pivotal Study: Part 2 (n=150)

- Enrolment began after DSMB recommendation and includes exposure on any part of the body
 - Persons with exposures to face, neck, hands, fingers eligible if present within 24 hours of bite
- DCGI permission for enrolment of children – 21 Aug 2013
- DCGI permission for enrolment of women of child bearing age – 01 April 2014
- Enrolment completed in Dec 2014
- Completion of study participation - March 2015
- Primary endpoint met (data submitted for publication)
- No deaths or PEP failure reported
- Marketing authorization approval – Oct 2016

Conclusions

- Very cautious approach used throughout development
 - Global and local rabies isolates tested extensively in RFFIT
 - Demonstrated direct effect of PEP efficacy in animals with confirmed rabies exposure
- Preclinical and phase I study data provided basis for evaluation of SII RMAb in patients with suspected rabies exposure
- Initially only patients with category III exposure on lower extremity enrolled followed by evaluation in patients with any type of category III exposure after interim analysis
- No case of PEP failure or rabies during the study period
- Safe and effective monoclonal developed as a passive component for rabies PEP



Thank you